

DESCRIPTION

TITLE OF INVENTION: ERGOTHIONEINE-CONTAINING COMPOSITION FOR
PREVENTING OR IMPROVING MENOPAUSAL SYMPTOMS

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TECHNICAL FIELD

[0001]

The present invention relates to an ergothioneine-containing composition for
preventing or alleviating climacteric symptoms.

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BACKGROUND ART

[0002]

Climacteric symptoms are induced by a decline in the secretion of male or
female hormones. In females, these symptoms are caused by a decline in estrogen
secretion due to ovarian senescence and typically appear over about 2 to 10 years
around menopause. The symptoms include hot flashes, sweating, insomnia,
depression, urinary incontinence, hair loss, muscle pain, and osteoporosis. In males, a
decline in blood testosterone levels induces not only the above symptoms but also
additional symptoms such as a decline in erectile function, a decline in libido, urinary
dysfunction, and abnormal blood cholesterol metabolism.

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[0003]

To prevent and treat such climacteric symptoms, hormone replacement therapy,
non-steroidal formulations, and other approaches have been developed. Currently,
hormone replacement therapy is used as the most effective method. However, long-
term administration of hormones may cause side effects such as an increased risk of
cancer, headaches, and weight gain. Therefore, there is a strong demand for safer
ingredients that exhibit the effect of preventing or alleviating climacteric symptoms and
are suitable for daily consumption as foods or beverages.

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[0004]

Ergothioneine is an amino acid found in mushrooms and the like. L-
ergothioneine is present in nature. Patent Literature 1 discloses that a hair growth
effect was confirmed by applying an extract of mushroom fruiting bodies containing
ergothioneine, niacin, and pantothenic acid to the scalp.

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CITATION LIST

- Patent Literature

[0005]

Patent Literature 1: JP 2009-275027 A

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SUMMARY OF INVENTION

- Technical Problem

[0006]

However, Patent Literature 1 does not disclose the hair growth effect of ergothioneine alone or the effect on climacteric symptoms.

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[0007]

The present invention aims to provide a composition for preventing or alleviating climacteric symptoms.

- Solution to Problem

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[0008]

As a result of extensive studies to solve the above problem, the present inventors found that L-ergothioneine or a salt thereof has the effect of preventing or alleviating climacteric symptoms.

[0009]

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In other words, the present invention relates to, but is not limited to, the following compositions for preventing or alleviating climacteric symptoms.

(1) A composition for preventing or alleviating a climacteric symptom, containing ergothioneine or a salt thereof as an active ingredient.

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(2) The composition according to (1) above, wherein the climacteric symptoms include at least one symptom selected from the group consisting of muscle pain, a decline in erectile function, a decline in urogenital function, a reduction in amount and/or quality of scalp hair, and a decline in vitality.

(3) The composition according to (1) or (2) above, wherein the climacteric symptoms are andropausal symptoms.

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(4) The composition according to any one of (1) to (3) above, wherein the composition prevents or alleviates climacteric symptoms via an ATP-sensitive potassium channel.

(5) The composition according to any one of (1) to (4) above, wherein the composition inhibits phosphodiesterase 5 or phosphodiesterase 7A1.

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(6) The composition according to any one of (1) to (5) above, wherein the

composition is an oral composition.

(7) The composition according to any one of (1) to (6) above, wherein the composition is a food or beverage.

(8) The composition according to any one of (1) to (7) above, wherein the
 5 composition is labeled with at least one function selected from the group consisting of
 “preventing climacteric symptoms”, “alleviating climacteric symptoms”, “supporting
 hormonal decline in middle-aged and older people”, “improving reproductive function
 in middle-aged and older people”, “alleviating urinary dysfunction in middle-aged and
 older people”, “preventing hair loss in middle-aged and older people”, “alleviating hair
 10 loss in middle-aged and older people”, and “alleviating a decline in vitality in middle-
 aged and older people”.

(9) A method for preventing or alleviating a climacteric symptom, including
 administering ergothioneine or a salt thereof to a subject.

(10) Use of ergothioneine or a salt thereof for preventing or alleviating a
 15 climacteric symptom.

- Advantageous Effects of Invention

[0010]

The present invention can provide a composition for preventing or alleviating
 20 climacteric symptoms.

BRIEF DESCRIPTION OF DRAWINGS

[0011]

FIG. 1 is a graph showing the evaluation results of the inhibitory activity of L-
 25 ergothioneine against phosphodiesterase 5.

FIG. 2 is a graph showing the evaluation results of the inhibitory activity of L-
 ergothioneine against phosphodiesterase 7A1.

FIG. 3 is a graph showing the evaluation results of the inhibitory activity of L-
 ergothioneine against substrate binding to ATP-sensitive potassium channels.

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DESCRIPTION OF EMBODIMENTS

[0012]

The composition for preventing or alleviating climacteric symptoms of the
 present invention contains ergothioneine or a salt thereof as an active ingredient.

35 Hereinbelow, the composition for preventing or alleviating climacteric symptoms of the

present invention is also referred to as the composition of the present invention.

Ergothioneine is a type of sulfur-containing amino acid. In the present invention, ergothioneine is preferably L-ergothioneine.

The salt of ergothioneine is not limited as long as it is a pharmacologically acceptable salt or a dietarily acceptable salt, and it may be either an acid salt or a basic salt. Examples of the acid salt include inorganic acid salts such as hydrochloride, sulfate, nitrate, and phosphate; and organic acid salts such as acetate, citrate, maleate, malate, oxalate, lactate, succinate, fumarate, and propionate. Examples of the basic salt include alkali metal salts such as sodium salt and potassium salt, and alkaline earth metal salts such as calcium salt and magnesium salt.

[0013]

Ergothioneine or a salt thereof is not limited in any way by its form, production method, or the like. Ergothioneine or a salt thereof that can be used may be a chemically synthesized product or a purified extract of a natural product. L-ergothioneine is abundantly present in golden/yellow oyster mushrooms (scientific name: *Pleurotus cornucopiae* var. *citrinopileatus*) belonging to the genus *Pleurotus* of the family *Pleurotaceae*. L-ergothioneine is also present in mushrooms such as common mushrooms (scientific name: *Agaricus bisporus*) including white button mushrooms, cremini mushrooms, and portabella mushrooms; grey oyster mushrooms (scientific name: *Pleurotus ostreatus*), shiitake (scientific name: *Lentinula edodes*), hen-of-the-woods (scientific name: *Grifola Frondosa*), reishi mushrooms (scientific name: *Ganoderma lucidum*), lion's mane mushrooms (scientific name: *Hericium erinaceus*), Yanagi-matsutake (scientific name: *Agrocybe aegerita*), girolles (scientific name: *Cantharellus cibarius*), porcini mushrooms (scientific name: *Boletus edulis*), and common morel mushrooms (scientific name: *Morchella esculenta*). When L-ergothioneine is obtained from a natural product, preferably, it is extracted from a golden/yellow oyster mushroom, for example. Ergothioneine or a salt thereof can also be produced by microbial fermentation. Ergothioneine or a salt thereof may be in an isolated form.

[0014]

L-ergothioneine or a salt thereof is present in natural products as well as food and beverages. These are compounds that have been consumed. Thus, for example, long-term ingestion of ergothioneine or a salt thereof is less likely to cause problems in terms of safety. The present invention can provide a highly safe composition for preventing or alleviating climacteric symptoms.

[0015]

Climacteric symptoms, induced by a decline in the secretion of male or female hormones, are diverse. Thus, the composition for preventing or alleviating climacteric symptoms desirably exerts multiple effects.

5 The climacteric symptoms preferably include at least one symptom selected from the group consisting of muscle pain, a decline in erectile function, a decline in urogenital function, a reduction in amount and/or quality of scalp hair, and a decline in vitality. The decline in urogenital function may be, for example, urinary dysfunction. The decline in vitality refers to a reduction in mental or physical energy. In the present
10 invention, the climacteric symptoms may be andropausal symptoms or menopausal symptoms, and are preferably andropausal symptoms. The andropausal symptoms include, but are not limited to, the symptoms described above.

[0016]

As described in EXAMPLES below, L-ergothioneine exhibited the inhibitory
15 activity against substrate binding to ATP-sensitive potassium (K_{ATP}) channels. In addition, L-ergothioneine has the effect of inhibiting phosphodiesterase 5 (PDE5) and phosphodiesterase 7A1 (PDE7A1).

It is known that the opening of vascular smooth muscle ATP-sensitive potassium channels improves blood flow to hair tissues. In addition, the opening of
20 mitochondrial ATP-sensitive potassium channels has been found to suppress apoptosis of hair matrix cells. Furthermore, the opening of ATP-sensitive potassium channels has been found to promote the proliferation of dermal papilla cells. Therefore, ergothioneine or a salt thereof can alleviate a reduction in amount and/or quality of scalp hair via K_{ATP} channels.

25 [0017]

PDE5 inhibition suppresses the degradation of cGMP, which is involved in relaxation of vascular smooth muscle, thereby leading to the effect of inducing vasodilation and smooth muscle relaxation. This effect is known to enhance blood flow and oxygen delivery, alleviating urinary dysfunction associated with benign
30 prostatic hyperplasia and erectile dysfunction. Furthermore, PDE5 inhibition has been reported to reduce muscle damage after treadmill running and improve endurance performance in mice (J Appl Physiol (1985), 2019 Jun 1; 126(6): 1737-1745). As described above, PDE5 inhibition enables prevention or alleviation of a decline in erectile function, a decline in urogenital function, and a decline in vitality.
35 Ergothioneine or a salt thereof can prevent or alleviate a decline in erectile function, a

decline in urogenital function, and a decline in vitality through PDE5 inhibition.

[0018]

PDE7A1 inhibition is known to suppress cytokine production and lead to anti-inflammatory effects. In addition, inhibition of substrate binding to K_{ATP} channels is known to open the K_{ATP} channels, leading to vasodilation. With inflammation suppressed, muscle pain can be prevented or alleviated. Also, vasodilation improves blood flow, which is considered to prevent or alleviate muscle pain. Thus, ergothioneine or a salt thereof can prevent or alleviate muscle pain through PDE7A1 inhibition and/or through mechanisms involving K_{ATP} channels.

10 [0019]

The composition of the present invention is used for preventing or alleviating climacteric symptoms. The phrase “preventing symptoms” as used herein encompasses suppressing the onset, delaying the onset, reducing the incidence rate, reducing the risk of onset, and the like. The phrase “alleviating symptoms” encompasses helping a subject recover from the symptoms, alleviating the symptoms, making positive changes in the symptoms, delaying or suppressing progression of the symptoms, and the like. The recovery encompasses partial recovery.

15 [0020]

The composition of the present invention may be an oral composition or a parenteral composition, preferably an oral composition.

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The oral composition may specifically be a food or beverage, an oral pharmaceutical product, an oral quasi-pharmaceutical product, feed, or the like, preferably a food or beverage or an oral pharmaceutical product, more preferably a food or beverage. The composition of the present invention may be a material, preparation, or the like to be added to a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like.

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[0021]

The composition of the present invention is applicable for therapeutic use (medical use) and non-therapeutic use (non-medical use). The “non-therapeutic” is a concept that does not include medical activities, i.e., a concept that does not include methods of surgery, therapy, or diagnosis of humans.

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[0022]

The composition of the present invention can contain optional additives and optional components in addition to ergothioneine or a salt thereof, as long as the effects of the present invention are not impaired. Such additives and components can be

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selected according to the composition form or the like. When the composition of the present invention is provided as an oral composition, the composition may contain any additives and the like that can be commonly used for oral compositions such as food and beverages, pharmaceutical products, quasi-pharmaceutical products, feed, and the like.

[0023]

When the composition of the present invention is provided as a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like, any common method can be used for production.

The oral composition of the present invention may be in any form such as a solid (e.g., powder, granule, tablet), a liquid, or a paste.

[0024]

For example, when the composition of the present invention is provided as a food or beverage, components usable in food or beverages (e.g., food materials and optional food additives) can be added to ergothioneine or a salt thereof to provide various food or beverages. The food or beverage is not limited. Examples thereof include general food or beverages, health foods, health supplements, health drinks, foods with function claims, foods for specified health uses, and foods for the sick. The health foods, health supplements, foods with function claims, foods for specified health uses, and the like can be used in various forms of preparations such as fine granules, tablets, granules, powders, capsules, chewable tablets, dry syrups, syrups, liquid agents, beverages, energy drinks, and liquid foods.

[0025]

When the composition of the present invention is provided as a pharmaceutical product or a quasi-pharmaceutical product, for example, a pharmacologically acceptable carrier, an optional additive, or the like can be added to ergothioneine or a salt thereof to provide various dosage forms of pharmaceutical products or quasi-pharmaceutical products. Such a carrier, additive, or the like may be any pharmacologically acceptable one that can be used in pharmaceutical products or quasi-pharmaceutical products. Examples thereof include excipients, binders, disintegrants, lubricants, antioxidants, and colorants. One or more of these can be used. The form of administration (ingestion) of the pharmaceutical product or the quasi-pharmaceutical product may be oral or parenteral (e.g., transdermal, transmucosal, enteral, or injection) administration. When the composition of the present invention is provided as a pharmaceutical product or a quasi-pharmaceutical product, it is preferably an oral

pharmaceutical product or an oral quasi-pharmaceutical product. Examples of dosage forms for oral administration of a pharmaceutical product or a quasi-pharmaceutical product include liquids, tablets, powders, fine granules, granules, sugar-coated tablets, capsules, suspensions, emulsions, and chewable tablets. Examples of the dosage forms for parenteral administration include injections, intravenous agents, ointments, lotions, adhesive skin patches, suppositories, nasal agents, and transpulmonary agents (inhalants).

[0026]

The subject (administration subject) who ingests the composition of the present invention or to whom the composition is administered is not limited. The administration subject is preferably a human.

In one embodiment, the administration subject may be, for example, a subject needing or wanting to prevent or alleviate climacteric symptoms. Examples of such a subject include middle-aged and older people. In one embodiment, the composition of the present invention is suitable as a composition for middle-aged and older people, for preventing or alleviating climacteric symptoms. The term “middle-aged and older people” includes the elderly. The elderly may be people who are 60 years old and older or 65 years old and older, for example. The middle-aged and older people may be those who are 40 years old and older, for example. In one embodiment, people who are 40 years old and older but 70 years old and younger are preferred subjects among the middle-aged and older people. The administration subject may be a healthy person. For example, the composition of the present invention can be used in healthy people for purposes such as preventing or alleviating climacteric symptoms. In the present invention, particularly preferred subjects are healthy people who are 45 years old and older but 65 years old and younger.

[0027]

The amount of ergothioneine or a salt thereof in the composition of the present invention is not limited and can be set according to the form of the composition or the like.

The amount of ergothioneine or a salt thereof in the composition of the present invention in terms of ergothioneine is, for example, preferably 0.0001% by weight or more, more preferably 0.001% by weight or more, while preferably 90% by weight or less, more preferably 50% by weight or less.

In one embodiment, the amount of ergothioneine or a salt thereof in the composition of the present invention in terms of ergothioneine is preferably 0.0001 to

90% by weight, more preferably 0.001 to 50% by weight. The amount of ergothioneine or a salt thereof can be measured by high-performance liquid chromatography (HPLC).

[0028]

5 Herein, in the case of ergothioneine, the expression regarding the amount of ergothioneine or a salt thereof in terms of ergothioneine or an expression similar thereto refers to the amount of ergothioneine; whereas in the case of a salt of ergothioneine, the expression or an expression similar thereto refers to a value obtained by multiplying the number of moles of the salt by the molecular weight of ergothioneine.

10 [0029]

 The composition of the present invention can be ingested or administered using an appropriate method depending on the form thereof. In one embodiment, preferably, the composition of the present invention is orally ingested (orally administered). The administration amount (intake) of the composition of the present invention is not limited.

15 The administration amount may be any amount sufficient to achieve the effect of preventing or alleviating climacteric symptoms and may appropriately be set according to the form of administration, administration method, the weight of the subject, and the like.

[0030]

20 In one embodiment, when the composition of the present invention is ingested by or administered to a human (adult) as a subject, the administration amount of ergothioneine or a salt thereof (in terms of ergothioneine) per day is preferably 2 mg or more, more preferably 5 mg or more, still more preferably 7 mg or more, while preferably 50 mg or less, more preferably 25 mg or less, still more preferably 20 mg or less. In one embodiment, the administration amount of the composition of the present invention as the amount of ergothioneine or a salt thereof (in terms of ergothioneine) to a human (adult) per day is preferably 2 to 50 mg, more preferably 5 to 25 mg, still more preferably 5 to 20 mg, further more preferably 7 to 20 mg. Preferably, the compound in the above amount is ingested or administered in one or more portions per day, for
30 example, in one to several portions (e.g., two or three portions) per day. In one embodiment, preferably, ergothioneine or a salt thereof in the above amount is orally ingested by or administered to a human. The above administration amount may be an administration amount per 60 kg body weight. In one embodiment, the composition of the present invention can be used to enable daily ingestion or administration of
35 ergothioneine or a salt thereof in the above amount to a human per 60 kg body weight,

for example.

[0031]

The amount of ergothioneine or a salt thereof in the composition of the present invention per adult daily intake is preferably 2 to 50 mg, more preferably 5 to 25 mg, still more preferably 5 to 20 mg, particularly preferably 7 to 20 mg, in terms of ergothioneine.

[0032]

The composition of the present invention may, for example, be labeled with a function of preventing or alleviating climacteric symptoms or a function resulting from the above function. The label may indicate the function of, for example, preventing or alleviating muscle pain; preventing or alleviating a decline in erectile function; preventing or alleviating a decline in urogenital function; preventing or alleviating a reduction in amount and/or quality of scalp hair; or preventing or alleviating a decline in vitality.

The composition of the present invention may, for example, be labeled with at least one function selected from the group consisting of “preventing climacteric symptoms”, “alleviating climacteric symptoms”, “supporting hormonal decline in middle-aged and older people”, “improving reproductive function in middle-aged and older people”, “alleviating urinary dysfunction in middle-aged and older people”, “preventing hair loss in middle-aged and older people”, “alleviating hair loss in middle-aged and older people”, and “alleviating a decline in vitality in middle-aged and older people”.

In one embodiment, preferably, the composition of the present invention is a food or beverage labeled with one or more functions described above. The label may be one indicating use of the composition for obtaining the function. The label may be attached to the composition itself, or may be attached to a container or package of the composition.

[0033]

As described above, ergothioneine or a salt thereof inhibits substrate binding to K_{ATP} channels. Thus, ergothioneine or a salt thereof can also be used as an active ingredient for inhibiting substrate binding to K_{ATP} channels. A composition for inhibiting substrate binding to K_{ATP} channels that contains ergothioneine or a salt thereof as an active ingredient is also an embodiment of the present invention.

Ergothioneine or a salt thereof inhibits phosphodiesterase 5 or phosphodiesterase 7A1. Thus, ergothioneine or a salt thereof can also be used as an

active ingredient for inhibiting phosphodiesterase 5 or an active ingredient for inhibiting phosphodiesterase 7A1. A composition for inhibiting phosphodiesterase 5 that contains ergothioneine or a salt thereof as an active ingredient is also an embodiment of the present invention. A composition for inhibiting phosphodiesterase 7A1 that
5 contains ergothioneine or a salt thereof as an active ingredient is also an embodiment of the present invention.

[0034]

The present invention also encompasses the following method:
a method for preventing or alleviating climacteric symptoms, including
10 administering ergothioneine or a salt thereof to a subject.

The method may be therapeutic or non-therapeutic.

[0035]

The present invention also encompasses the following use:
use of ergothioneine or a salt thereof for preventing or alleviating climacteric
15 symptoms.

The use may be therapeutic or non-therapeutic.

Administering ergothioneine or a salt thereof to a subject enables prevention or alleviation of climacteric symptoms.

[0036]

20 In the above method and use, the preferred embodiments of ergothioneine or a salt thereof are the same as described above for the composition of the present invention. Ergothioneine or a salt thereof may include one type of ergothioneine or a salt thereof or two types of ergothioneine or a salt thereof. In the above method and use, preferably, ergothioneine or a salt thereof is administered to (ingested by) a subject at least once a
25 day, for example, one to several times (e.g., two or three times) a day. In the above method and use, ergothioneine or a salt thereof is preferably orally administered (ingested). The above use is preferably for humans.

[0037]

In the above method and use, ergothioneine or a salt thereof is simply used in
30 an amount (effective amount) sufficient to achieve a desired effect. The preferred administration amount of ergothioneine or a salt thereof, preferred administration subjects, and the like are as described above for the composition of the present invention. Ergothioneine or a salt thereof may be administered directly or may be administered in the form of a composition containing the ergothioneine or a salt thereof.
35 For example, the composition of the present invention described above may be used.

[0038]

The present invention encompasses use of ergothioneine or a salt thereof for producing a composition for preventing or alleviating climacteric symptoms.

5 The present invention also relates to ergothioneine or a salt thereof for use in preventing or alleviating climacteric symptoms.

[0039]

10 The numerical range defined by the lower limit and the upper limit herein, i.e., “the lower limit to the upper limit”, includes the lower limit and the upper limit. For example, the range defined by “1 to 2” means 1 or more and 2 or less, with 1 and 2 being included. Herein, the range may be any combination of any upper limit and any lower limit.

EXAMPLES

[0040]

15 The present invention is described in further detail below with reference to examples. The present invention is not limited to these examples.

[0041]

<Example 1>

(Evaluation of phosphodiesterase inhibitory activity)

20 To evaluate the molecular targets of L-ergothioneine, in vitro assays were conducted on phosphodiesterase 5 (PDE5) and phosphodiesterase 7A1 (PDE7A1). The in vitro assays were outsourced to Eurofins Panlabs and performed according to the following procedure.

[0042]

25 (PDE5)

PDE5 (Eurofins Cerep) isolated from human platelets was used. The PDE5 in an amount of 60 ng was incubated at 22°C for 30 minutes with L-ergothioneine (L-ergothioneine concentration: 100 μ M or 1000 μ M) in a buffer containing 44 mM Tris/HCl (pH 7.4), 3 mM MgCl₂, 1.04 mM dithiothreitol (DTT), 0.03% bovine serum albumin (BSA), 2% glycerol, 200 mM NH₄Cl, and 0.1 μ M Ci[³H]cGMP.

30 Phosphodiesterase SPA beads (Product No.: RPNQ0150, PerkinElmer) were added, and then luminescence was measured using a detector. Based on the amounts of [³H]5'GMP, the inhibitory activity of L-ergothioneine was evaluated. The amount of [³H]5'GMP in the reaction solution without L-ergothioneine was defined as 100% PDE5

35 activity, and the relative PDE5 activity (%) relative to the control was calculated based

on the amount of [^3H]5'GMP in the reaction solution containing L-ergothioneine. The inhibitory activity (%) was calculated from the following formula.

Inhibitory activity (%) = $100 - (\text{relative PDE5 activity in the presence of L-ergothioneine})$

5 [0043]

(PDE7A1)

Human recombinant PDE7A1 expressed in insect cells (Eurofins Cerep) was used. The PDE7A1 at an activity of 0.6 U was incubated at 22°C for 30 minutes with L-ergothioneine (L-ergothioneine concentration: 100 μM or 1000 μM) in a buffer
 10 containing 40 mM Tris/HCl (pH 7.4), 8 mM MgCl_2 , and 0.035 μM $\text{Ci}[^3\text{H}]\text{cAMP}$. Phosphodiesterase SPA beads (Product No.: RPNQ0150, PerkinElmer) were added, and then luminescence was measured using a detector. Based on the amounts of [^3H]5'AMP, the inhibitory activity of L-ergothioneine was evaluated. The amount of [^3H]5'AMP in the reaction solution without L-ergothioneine was defined as 100%
 15 PDE7A1 activity, and the relative PDE7A1 activity (%) relative to the control was calculated based on the amount of [^3H]5'AMP in the reaction solution containing L-ergothioneine. The inhibitory activity (%) was calculated from the following formula.
 Inhibitory activity (%) = $100 - (\text{relative PDE7A1 activity in the presence of L-ergothioneine})$

20 [0044]

FIG. 1 is a graph showing the evaluation results of the inhibitory activity of L-ergothioneine against phosphodiesterase 5. FIG. 2 is a graph showing the evaluation results of the inhibitory activity of L-ergothioneine against phosphodiesterase 7A1. The concentration (μM) along the horizontal axis in each of FIG. 1 and FIG. 2 indicates
 25 the concentration of L-ergothioneine. L-ergothioneine exhibited inhibitory activity against PDE5 and PDE7A1. PDE5 is known to exert the effect of inducing vasodilation and smooth muscle relaxation to enhance blood flow and oxygen delivery, alleviating a decline in urogenital function such as urinary dysfunction associated with benign prostatic hyperplasia and a decline in erectile dysfunction. Also, PDE5
 30 inhibition is known to improve endurance performance, and thus presumably prevents or alleviates a decline in vitality at the climacteric.

Moreover, PDE7A1 inhibition is known to suppress cytokine production and lead to anti-inflammatory effects, preventing or alleviating muscle pain. Thus, L-ergothioneine presumably achieves the above effects through inhibition of PDE5 and
 35 PDE7A1.

[0045]

<Example 2>

(Evaluation of inhibitory activity against substrate binding to ATP-sensitive potassium channels)

5 To evaluate the molecular targets of L-ergothioneine, an in vitro assay was conducted on ATP-sensitive potassium (K_{ATP}) channels. The in vitro assay was outsourced to Eurofins Panlabs and performed according to the following procedure.

[0046]

10 A membrane fraction (containing K_{ATP} channels, available from Eurofins Cerep) in an amount of 400 μ g from rat cerebral cortex was incubated at 22°C for 60 minutes in a 50 mM Tris-HCl buffer (pH 7.4) with 0.1 nM [3 H]glibenclamide and L-ergothioneine (L-ergothioneine concentration: 100 μ M or 1000 μ M). Glibenclamide is a K_{ATP} channel inhibitor. Nonspecific binding was determined in the presence of 1 μ M glibenclamide (without L-ergothioneine). Since excess glibenclamide prevents
15 [3 H]glibenclamide from binding to K_{ATP} channels, the radioactivity detected therein represents nonspecific binding. The membrane fraction was filtered and washed, and the substrate-binding inhibitory activity of L-ergothioneine was evaluated based on the measured radioactivity. A larger amount of [3 H]glibenclamide binding to K_{ATP} channels results in higher radioactivity in the membrane fraction.

20 [0047]

FIG. 3 is a graph showing the evaluation results of the inhibitory activity of L-ergothioneine against substrate binding to ATP-sensitive potassium channels. The concentration (μ M) along the horizontal axis indicates the concentration of L-ergothioneine.

25 The inhibitory activity (%) against substrate binding to K_{ATP} channels was determined by the following procedure. From the radioactivity of the membrane fraction in the reaction solution without L-ergothioneine (control) taken as 100% and the radioactivity of the membrane fraction in the reaction solution with L-ergothioneine, the relative activity (%) of the membrane fraction in the reaction solution with L-
30 ergothioneine (100 μ M or 1000 μ M) relative to the control was determined. When the binding of glibenclamide to K_{ATP} channels is inhibited by L-ergothioneine, the radioactivity of the membrane fraction decreases. The inhibitory activity (%) against substrate binding to K_{ATP} channels was determined by subtracting the relative activity (%) of the membrane fraction with L-ergothioneine from the radioactivity (100%) of the
35 membrane fraction in the control.

[0048]

L-ergothioneine exhibited inhibitory activity against the binding of glibenclamide as a substrate to K_{ATP} channels. It is known that the opening of vascular smooth muscle ATP-sensitive potassium channels improves blood flow to hair tissues.

5 In addition, the opening of mitochondrial ATP-sensitive potassium channels has been found to suppress apoptosis of hair matrix cells. Furthermore, the opening of ATP-sensitive potassium channels has been found to promote the proliferation of dermal papilla cells. Thus, L-ergothioneine presumably alleviates a reduction in amount and/or quality of scalp hair via ATP-sensitive potassium channels.

10 In addition, inhibition of substrate binding to K_{ATP} channels is known to open the K_{ATP} channels, leading to vasodilation. Vasodilation improves blood flow, which is considered to prevent or alleviate muscle pain. Thus, L-ergothioneine presumably prevents or alleviates muscle pain via ATP-sensitive potassium channels.

CLAIMS

Claim 1. A composition for preventing or alleviating a climacteric symptom, comprising ergothioneine or a salt thereof as an active ingredient.

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Claim 2. The composition according to claim 1,
wherein the climacteric symptoms include at least one symptom selected from the group consisting of muscle pain, a decline in erectile function, a decline in urogenital function, a reduction in amount and/or quality of scalp hair, and a decline in vitality.

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Claim 3. The composition according to claim 1 or 2,
wherein the climacteric symptoms are andropausal symptoms.

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Claim 4. The composition according to claim 1 or 2,
wherein the composition prevents or alleviates climacteric symptoms via an ATP-sensitive potassium channel.

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Claim 5. The composition according to claim 1 or 2,
wherein the composition inhibits phosphodiesterase 5 or phosphodiesterase 7A1.

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Claim 6. The composition according to claim 1 or 2,
wherein the composition is an oral composition.

Claim 7. The composition according to claim 6,
wherein the composition is a food or beverage.

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Claim 8. The composition according to claim 1 or 2,
wherein the composition is labeled with at least one function selected from the group consisting of “preventing climacteric symptoms”, “alleviating climacteric symptoms”, “supporting hormonal decline in middle-aged and older people”, “improving reproductive function in middle-aged and older people”, “alleviating urinary dysfunction in middle-aged and older people”, “preventing hair loss in middle-aged and older people”, “alleviating hair loss in middle-aged and older people”, and

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“alleviating a decline in vitality in middle-aged and older people”.

Claim 9. A method for preventing or alleviating a climacteric symptom, comprising administering ergothioneine or a salt thereof to a subject.

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Claim 10. Use of ergothioneine or a salt thereof for preventing or alleviating a climacteric symptom.